(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 3-7, 9, 10, 12, 13, and 49
Claims allowed:	(none)
Claims objected to:	Claims 3-7, 9, 10, 12, 13, and 49
Claims canceled:	Claims 8, 17-27, and 30-45
Claims withdrawn:	Claims 1, 2, 11, 14-16, 28-29[1], and 46-48
Claims on Appeal:	Claims 3-7, 9, 10, 12, 13, and 49 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a polynucleotide encoding a polypeptide ("PAWES-2") containing a region similar to a Type I EGF motif signature and containing two cysteine residues characteristic of this motif. The polynucleotide has a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of PAWES-2, for toxicology testing, and for drug discovery (see the Specification at, e.g., page 38, line 12 through page 41, line 27). As described in the Specification (page 17, lines 10-30):

> Nucleic acids encoding the PAWES-2 of the present invention were first

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[1]Appellants note that Claims 28 and 29 were not listed in any category on the Office Action Summary (page 1) of the Final Office Action. Appellants assume that the omission of Claims 28 and 29 from the listing of "withdrawn claims" on the Office Action Summary was inadvertent.

identified in Incyte Clone 2056178 from the bronchial epithelium cDNA library (BEPINOT01) using a computer search, e.g., BLAST, for amino acid sequence alignments. A consensus sequence, SEQ ID NO:4, was derived from the following overlapping and/or extended nucleic acid sequences: Incyte Clones 2056178 and 2056018 (BEPINOT01), 826303 (PROSNOT06), 1981527 (LUNGTUT03), 1511001 (LUNGNOT14), and 642949 (BRSTTUT02).

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:3, as shown in Figures 2A, 2B, 2C, 2D, and 2E. PAWES-2 is 332 amino acids in length and has one potential N-glycosylation site at N286; two potential cAMP- and cGMP-dependent protein kinase phosphorylation sites at T203 and T235; seven potential casein kinase II phosphorylation sites at S33, S77, S93, T147, T175, T237, and T310; two potential protein kinase C phosphorylation sites at S113 and S241; and a potential signal peptide sequence from M1 to A39. In addition, the region of PAWES-2 from N285 to H300 is similar to a Type I EGF motif signature and contains two cysteine residues characteristic of this motif. A region of unique sequence in PAWES-2 from about amino acid 50 to about amino acid 59 is encoded by a fragment of SEQ ID NO:4 from about nucleotide 689 to about nucleotide 718. Northern analysis shows the expression of this sequence in various libraries, at least 73% of which are associated with cancerous or proliferating tissue and at least 33% of which involve immune response. In particular, 40% of the libraries expressing PAWES-2 are derived from reproductive tissue, 20% are derived from cardiovascular tissue, and 13% are derived from gastrointestinal tissue.

(6) ISSUES

1. Whether Claims 3-7, 9-10, 12-13, and 49, directed to a polynucleotide encoding a PAWES-2 polypeptide, meets the utility requirement of 35 U.S.C. §101.

2. Whether one of ordinary skill in the art would know how to use a polynucleotide of Claims 3-7, 9-10, 12-13, and 49, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, with respect to the utility rejection.

3. Whether one of ordinary skill in the art would know how to use a polynucleotide of Claims 3-7, 9-10, and 12-13, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, with respect to naturally occurring sequences.

4. Whether one of ordinary skill in the art would know how to use a polynucleotide of Claims 3-7 and 9-10, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, with respect to expressed sequences and expressed polypeptides.

5. Whether one of ordinary skill in the art would know how to make and use a polynucleotide of Claims 3-4, 6-7, 9-10, and 12-13, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, with respect to polynucleotides encoding polypeptide variants, polynucleotides encoding SEQ ID NO:3, polynucleotides encoding a polypeptide fragment, polynucleotide variants, and complementary polynucleotides.

6. Whether the polynucleotides encoding SEQ ID NO:3, the polynucleotides encoding polypeptide variants, the polynucleotides encoding immunogenic fragments, the polynucleotide variants, the polynucleotide fragments, and the complementary polynucleotides of Claims 3-7, 9-10, and 2-13 meet the written description requirement of 35 U.S.C. §112, first paragraph.

7. Whether a polynucleotide of Claims 3, 6, 7, and 9 is anticipated by U.S. Patent No. 5,683,898.

(7) GROUPING OF THE CLAIMS

As to Issue 1

This issue pertains to Claims 3-7, 9-10, 12-13, and 49.

As to Issue 2

This issue pertains to Claims 3-7, 9-10, 12-13, and 49.

As to Issue 3

This issue pertains to Claims 3-7, 9-10, and 12-13.

As to Issue 4

This issue pertains to Claims 3-7 and 9-10.

As to Issue 5

This issue pertains to Claims 3-4, 6-7, 9-10, and 12-13

As to Issue 6

This issue pertains to Claims 3-7, 9-10, and 12-13.

As to Issue 7

This issue pertains to Claims 3, 6, 7, and 9.

(8) APPELLANTS' ARGUMENTS

Issue One: Utility Rejection

Claims 3-7, 9-10, 12-13, and 49 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The Final Office Action maintains the rejection made in the Office Action mailed December 31, 2002 which alleges in particular that "the claimed invention is not supported by a specific asserted utility, a substantial utility, or a well established utility." (Office Action mailed December 31, 2002, page 5.)

The rejection of Claims 3-7, 9-10, 12-13, and 49 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide corresponding to a gene that is expressed in human bronchial epithelium tissue. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Appellants previously submitted on March 31, 2003 the First Declaration of Dr. Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The First Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The First Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on April 29, 1998] that cDNA microarrays that contained the SEQ ID NO:4 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity. (First Bedilion Declaration, ¶ 15.)

Appellants further submit with this brief three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references. The Rockett Declaration, a second Bedilion Declaration, Iyer Declaration, and the ten (10) references fully establish that, prior to the April 29, 1998 filing date of the priority Hillman '725 application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

Appellants file herewith:

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");
2. the Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Second Bedilion Declaration");
3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and

4. ten (10) references published before the April 29, 1998 filing date of the priority Hillman '725 application,:

a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995) (Reference No. 1)

b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995) (Reference No. 2)

c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (Reference No. 3)

d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (Reference No. 4)

e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996) (Reference No. 5)

f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (Reference No. 6)

g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997) (Reference No. 7)

h) Acacia Biosciences Press Release (August 11, 1997) (Reference No. 8)

i) V. Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (September 15, 1997) (Reference No. 9)

j) J. L. DeRisi et al., Exploring the metabolic and genetic control of gene expression on a genomic scale, Science 278:680 - 686 (October 24, 1997) (Reference No. 10)

The law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the First Bedilion Declaration, the Rockett Declaration,

the Second Bedilion Declaration, and the Iyer Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the encoded polypeptide. The uses of the claimed polynucleotide for gene expression monitoring applications including toxicology testing are in fact independent of the precise function of the encoded polypeptide.

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the priority Hillman '725 application relating to the use of the SEQ ID NO:4 polynucleotide for gene expression monitoring applications. Such gene expression monitoring applications are highly useful in drug development and in toxicity testing.

The Examiner's new positions and arguments include that the use of the SEQ ID NO:4 polynucleotide in a gene expression monitoring experiment would be insufficient to constitute substantial, specific, and credible utility allegedly because "[d]etection of SEQ ID NO:4 under specific conditions using a claimed microarray would merely be an invitation to experiment further to determine what that result means"[2] (Final Office Action, e.g., page 4) and that "the result would not be informative." (Final Office Action, page 5.) Indeed, the Final Office Action fails to acknowledge, let alone address, the priority Hillman '725 disclosure that microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents." (Hillman '725 application at page 41, lines 10-11 and 13-14.) The Final Office Action further discounts the previously submitted First Bedilion Declaration, stating that the First Bedilion Declaration's arguments are "not deemed persuasive." (Final Office Action, page 3.) The Final Office Action further discounts the evidence of the Rockett et al. Xenobiotica paper (Exhibit C attached to the Rockett Declaration, cited previously in the Response filed March 31, 2003), alleging that "[t]he Rockett et al paper (Xenobiotica, 1999, 29(7):655-691), however, supports the Examiner's

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[2]The Examiner uses the term "claimed microarray" in the above quoted passage. (Final Office Action, page 4.) Appellants note that the claims on appeal do not recite "microarray." Appellants assume that the Examiner used the term "claimed microarray" inadvertently.

assertion that the use of the claimed nucleic acids in microarrays does not meet the requirement of being specific and substantial." (Final Office Action, pages 9-10.)

Under the circumstances, Appellants are submitting with this Appeal Brief (in triplicate) Declarations under 37 C.F.R. § 1.132 of John C. Rockett, Ph.D. (hereinafter the "Rockett Declaration"), of Tod Bedilion, Ph.D. (hereinafter "the Second Bedilion Declaration"), and of Vishwanath R. Iyer, Ph.D. (hereinafter the "Iyer Declaration"), and ten (10) references published before the April 29, 1998 filing date of the priority Hillman '725 application. As we will show, the Rockett Declaration, the Second Bedilion Declaration, the Iyer Declaration, and the accompanying references show the many substantial reasons why the Examiner's new positions and arguments with respect to the use of the SEQ ID NO:4 polynucleotide in gene expression monitoring applications are without merit.

The fact that the Rockett Declaration, the Second Bedilion Declaration, the Iyer Declaration, and the accompanying references are being submitted in response to positions taken and arguments made for the first time in the Final Office Action, including arguments disregarding the persuasiveness of the First Bedilion Declaration, constitutes, by itself, "good and sufficient reasons" under 37 C.F.R. § 1.195 why those Declarations were not earlier submitted and should be admitted at this time. Appellants also note that the newly submitted Declarations and references are responsive to the new utility rejection as framed by the Board of Appeals in copending cases with similar issues.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of

serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the

Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Uses of the claimed polynucleotide for diagnosis of conditions and disorders characterized by expression of PAWES-2, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the previously submitted First Bedilion Declaration, and in the accompanying Rockett Declaration, Second Bedilion Declaration, Iyer Declaration, and the accompanying references.

A. The use of the claimed polynucleotide for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the previously submitted First Bedilion Declaration, and in the accompanying Rockett Declaration, Second Bedilion Declaration, Iyer Declaration, and the accompanying references. The claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his First Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the priority Hillman '725 application on April 29, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that

specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. (First Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications. (First Bedilion Declaration, ¶¶ 12 and 15).[3]

In connection with his explanations, Dr. Bedilion states that the "Hillman '725 application would have led a person skilled in the art on April 29, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cell proliferative disorders to conclude that a cDNA microarray that contained the SEQ ID NO:4 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:4 polynucleotide" (First Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on April 29, 1998] that cDNA microarrays that contained the SEQ ID NO:4 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-April 29, 1998 publications showing the state of the art on April 29, 1998. (First Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his First Declaration include more than two pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on April 29, 1998 (and for several years prior to April 29, 1998) "without

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[3]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the priority Hillman '725 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as northern analysis, that predated by many years the development of the cDNA technology (First Bedilion Declaration, ¶ 16).

any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the priority Hillman '725 application clearly include using differential gene expression analyses in toxicity studies (First Bedilion Declaration, ¶ 10).

Thus, the First Bedilion Declaration establishes that persons skilled in the art reading the priority Hillman '725 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:4 polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to April 29, 1998." (First Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the priority Hillman '725 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1998 would have understood that any expressed polynucleotide is useful for a number of gene expression monitoring applications, *e.g.*, in cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s . . . that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology. [Rockett Declaration, ¶ 18.][4]

In his Second Declaration, Dr. Bedilion explains why a person of skill in the art in 1998 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Second Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1998 would have

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[4]"Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

In addition, Dr. Rockett explains in his Declaration that "there are a number of other differential expression analysis technologies that precede the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, including: (1) differential screening; (2) subtractive hybridization, including variants such as chemical cross-linking subtraction, suppression-PCR subtractive hybridization and representational difference analysis; (3) differential display; (4) restriction endonuclease facilitated analyses, including serial analysis of gene expression (SAGE) and gene expression fingerprinting and (5) EST analysis." (Rockett Declaration, ¶ 7.)

Nowhere does the Patent Examiner address the fact that, as described on pages 41 and 51 of the priority Hillman '725 application, the claimed polynucleotide can be used as a highly specific probe in, for example, cDNA microarrays – a probe that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotide. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The First Bedilion Declaration shows that a number of pre-April 29, 1998 publications

confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the priority Hillman '725 application was filed (First Bedilion Declaration ¶¶ 10-14; First Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, First Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (First Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see First Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see [First Bedilion] Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published before or shortly after the filing of the priority Hillman '725 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up– or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes

> for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original)

John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Exhibit C attached to the Rockett Declaration, cited previously in the Response filed March 31, 2003):

In a pre-April 29, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Reference No. 11; cited previously in the Response filed March 31, 2003) (emphasis added).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his First Declaration and in the Rockett and Iyer Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., *supra* (Exhibit C attached to the Rockett Declaration, cited previously in the Response filed March 31, 2003):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Exhibit C attached to the Rockett Declaration, cited previously in the Response filed March 31, 2003, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 12, cited previously in the Response filed March 31, 2003); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 13, cited previously in the Response filed March 31, 2003).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 14, see page 683, cited previously in the Response filed March 31, 2003). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original

message to which she was responding (Reference No. 15, cited previously in the Response filed March 31, 2003), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7), the Acacia Biosciences Press Release (Reference No. 8), and the Glaser article (Reference No. 9).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function. . . . [abstract]
>
> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]
>
> The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy

animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof. [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

> It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]
>
> Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]
>
> Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Applicants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> [The invention provides a] method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens. [abstract]
>
> [W]e see each individual gene product as a 'pixel' of information, which relates to

the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]

The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]

High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]

The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]

The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]

The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [i.e., the results yield analogous data to microarrays] [page 8]

Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]

In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as "gene transcript image analysis" or "gene transcript frequency analysis". The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to different normal cells or tissues from diseased cells or tissues. . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models. [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]

[T]his research tool provides a way to get new drugs to the public faster and more

economically. [page 36]

In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]

[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 9, 1995, describes an expression profiling platform, the "genome reporter matrix," which is different from nucleic acid microarrays. Additionally describing the use of nucleic acid microarrays, the patent makes clear that the utility of comparing multidimensional expression data sets is independent of the methods by which such profiles are obtained.

The '588 patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

[The invention provides] methods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug. [abstract]

The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism. [column 1]

The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires

transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix. [column 2]

Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects. [columns 2-3]

Furthermore, it is not necessary to know the identity of any of the responding genes. [column 3]

[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical. [column 4]

The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters. [column 4]

A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included. [columns 6-7]

In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After

contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug. [columns 7-8]

In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile. [column 8]

The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses. [column 8]

Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli. [column 9]

The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s). [column 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (Reference No. 8), and the September 15, 1997 news report by Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (Reference No. 9), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), filed on October 11, 1996 and published on April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the WO 97/13877 publication describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> [T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates. [Field of the invention]
>
> An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems. [page 3]
>
> Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals. [page 3]
>
> The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity. [page 3]
>
> As used herein, the terms "gene expression profile," and "gene expression pattern" which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand. [page 7]
>
> The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . [page 7]

In light of this and other evidence of the state of the art, one of ordinary skill in the toxicology arts would conclude that "[i]t is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology." (Declaration of Dr. John C. Rockett, ¶ 18.)

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities. The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's rejection of the claimed invention is based in part on the ground that, without information as to the precise biological role or biological function of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological role or function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the First Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person

of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological role or function of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the family of expressed polypeptides, the Examiner refused to impute the utility of the members of the family of expressed polypeptides to PAWES-2.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses PAWES-2 as if the general class in which it is included is not the family of expressed polypeptides, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the family of expressed polypeptides do not. The family of expressed polypeptides is sufficiently specific to rule out any reasonable possibility that PAWES-2 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the PAWES-2 encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide also is useful.

C. Because the uses of the claimed polynucleotide in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. [First Bedilion Declaration at ¶ 15.]

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polypeptides and polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polypeptide or polynucleotide is dependent on the **identity** of that polypeptide or polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide or polynucleotide in toxicology testing is specific to both the compound being tested and the polypeptide polynucleotide used in the test. **No two**

human-expressed polypeptides or polynucleotides are interchangeable for toxicology testing because the effects on the expression of any two such polypeptides or polynucleotides will differ depending on the identity of the compound tested and the **identities** of the two polypeptides or polynucleotides. It is not necessary to know the biological functions and disease associations of the polypeptides or polynucleotides in order to carry out such toxicology tests. Therefore, at the very least, the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polypeptides or polynucleotides, and are clearly useful as such.

As an example, any histone gene or protein expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone gene or protein may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed histone gene or protein is surely an excellent subject for toxicology studies when developing drugs **targeted to other genes or proteins**. A drug candidate which alters expression of a histone gene or protein is toxic because disruption of such a pervasively-expressed gene or protein would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene or protein, measuring the expression of a histone gene or protein is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone gene or protein in toxicology testing is specific and substantial because a toxicology test using that histone gene or protein cannot be replaced by a toxicology test using a different gene, including any other histone gene or protein. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone gene or protein .

The expression of the SEQ ID NO:4 polynucleotide in human tissues would lead a skilled artisan to believe that this polynucleotide has some physiological implications, even if these implications have not been precisely identified. During toxicology testing, a change in expression of a human-expressed polynucleotide indicates potential toxicity of a drug candidate, even if the physiological implications of that polynucleotide or of the polypeptide encoded by that polynucleotide are unknown. Such a toxicology test allows one to choose a lead drug candidate which has minimal effects on the expression of proteins other than the protein to which

the candidate is targeted. Such a lead drug candidate would be less likely to have unintended side effects than a drug candidate having greater effects on the expression of genes/proteins other than the intended drug target. Thus, the benefit of such a toxicology test is an increased chance of finding a safe and effective drug, and a corresponding reduction in the expense and time of bringing a drug to market.

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (Specification, e.g., pages 38-41) and chromosomal mapping (Specification, e.g., pages 41-42).

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

1. Prediction of Protein Function Using Sequence Homology

While the Examiner has cited literature (Bowie et al., Burgess et al., and Lazar et al.) identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Careful review of the Bowie et al. reference reveals that the teachings of Bowie et al. are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. As discussed below in further detail, such experiments are not relevant to Appellants' use of amino acid sequence homology to reasonably predict protein function.

In support of Appellants' use of amino acid sequence homology reasonably to predict the utility of the claimed polypeptide, Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution (Bowie et al., page 1306, 1st column, last paragraph, and 2d column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph). It is known in the art that natural selection acts to conserve protein function. As taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits

these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection.

The Examiner further cited Lazar et al. and Burgess et al. as demonstrating "[t]hat even a single amino acid alteration can alter the function of a protein." (Final Office Action, page 19.) However, these references are not relevant to the case at hand. Lazar et al. describe the mutagenesis of two amino acid residues that are highly conserved among EGFs and TGFs. Similarly, Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. In both of these cases, particular amino acid residues with known importance to protein function were specifically targeted for site-directed mutagenesis. These mutations were "artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by Lazar et al. and Burgess et al. would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Therefore, the teachings of Lazar et al. and Burgess et al. are not relevant to the case at hand.

One could then argue that partial loss-of-function mutations do occur in nature, for example, the mutation in hemoglobin that causes sickle cell anemia. However, this example is the **rare** exception in evolution, **not the rule**. Persistence of such a mutation in a population would **not** be expected by one of ordinary skill in the art. Persistence occurs only because of the fluke of heterozygous advantage. Therefore, the Examiner's assertion that one of skill in the art would routinely expect to find single amino acid substitutions that drastically affect the function of the individual members of a conserved protein family is entirely unsubstantiated. Furthermore, in those rare cases where a partial loss-of-function mutation is persistent, the fact remains that the mutant polypeptide **still retains the utility of the non-mutant polypeptide**. The utility of the mutant polypeptide is the same as that of the non-mutant polypeptide, even though the results achieved are not equivalent. **Some** utility, not **perfect** utility, is all that is statutorily required for patentable utility.

The Examiner alleged that "it is well known in the art that even a single amino acid change will change the structure and the function of a protein." (Office Action mailed December 31, 2002, page 7.) However, in a recent Federal Circuit decision (Boehringer Ingelheim

Vetmedica, Inc. v. Schering-Plough Corporation and Schering Corporation; CAFC 02-1026, -1027, February 21, 2003), the Court stated that "the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence."

The literature cited by the Examiner is not inconsistent with the Appellants' proof of homology by a reasonable probability. It may show that Appellants cannot prove function by homology with **certainty**, but Appellants need not meet such a rigorous standard of proof. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

2. Biological function, differential expression, or disease association is irrelevant to utility

The Examiner states that "Applicants have disclosed no features or characteristics of the claimed SEQ ID NO:4, or the putative polypeptide encoded thereby, that would inform the experimenter as to what the significance of detecting that particular sequence would be" and "[i]n the absence of any known biological function, or association with any disease state or condition, . . . the use of the claimed nucleic acids in a microarrays is not specific or substantial." (Final Office Action, page 4.) The Examiner notes that "[b]iological function is one of the factors that might be disclosed in establishing utility, but it is not required." (Final Office Action, page 7.) The Examiner would also accept disease association or differential expression as adequate evidence of utility. (Final Office Action, e.g, at page 4, 7, and 16.) The Examiner however continues to ignores other utilities discussed in the Specification and/or well known in the art, such as toxicology testing, alleging that "[d]etection of SEQ ID NO:4 under specific conditions using a microarray would merely be an invitation to experiment further." (Final Office Action, page 8.)

Appellants have demonstrated a utility for the claimed SEQ ID NO:4 polynucleotide and the encoded SEQ ID NO:3 polypeptide irrespective of whether or not a person would wish to perform additional experimentation or characterization on biological function, disease association, or differential expression as another utility. The fact that additional experimentation could be performed to determine the biological function, disease association, or differential expression of the claimed SEQ ID NO:4 polynucleotide and the encoded SEQ ID NO:3 polypeptide does not preclude, and is in fact irrelevant to, the actual utility of the invention. That utility exists today regardless of the biological function, disease association, or differential expression of the claimed SEQ ID NO:4 polynucleotide and the encoded SEQ ID NO:3 polypeptide. (See, e.g, Rockett Declaration, ¶ 18, and Iyer Declaration, ¶ 9.)

Monitoring the expression of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polypeptide, regardless of the biological function or differential expression of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide. The claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is useful for measuring the toxicity of drug candidates specifically targeted to **other** polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide.

3. Use of the claimed polynucleotides in toxicology testing

The Final Office Action finds the First Bedilion Declaration "not persuasive," alleging that "[t]he fact that a microarray may have utility does not confer utility on any and all nucleic acids that might be assayed using the microarray." (Final Office Action, page 8.)

The Examiner's arguments amount to nothing more than the Examiner's disagreement with the First Bedilion Declaration and the Appellants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Appellants' expert. The Examiner must accept the Appellants' assertions to be true. The Examiner is, moreover, wrong on the facts because the First Bedilion Declaration demonstrates how one of skill in the art, reading the specification at the time the

priority Hillman '725 application was filed (April 29, 1998), would have understood that specification to disclose the use of the claimed polynucleotides in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the First Bedilion Declaration at, e.g., ¶¶ 10-16).

For example, monitoring the expression of the SEQ ID NO:4 polynucleotide is a method of testing the toxicology of drug candidates during the drug development process. Dr. Bedilion in his First Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets." (First Bedilion Declaration ¶ 10.) Thus, if the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

However, the Examiner continues to view the utility in toxicology testing of the claimed polynucleotides as requiring knowledge of either the biological function or disease association of the claimed polynucleotides. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polynucleotides. The Examiner has refused to consider that the claimed polynucleotides are useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucleotides, but to **other** polynucleotides. This utility of the claimed polynucleotides does not require any knowledge of the biological function or disease association of the SEQ ID NO:3 polypeptide or SEQ ID NO:4 polynucleotide and is a specific, substantial and credible utility. (See, e.g, Rockett Declaration, ¶ 18, and Iyer Declaration, ¶ 9.)

4. Utility of all expressed polynucleotides in toxicology testing

The Examiner argues that use of the claimed polynucleotide in toxicology testing is "nonspecific and would apply to virtually every member of a general class of materials, such as DNA." (Final Office Action, page 12.) The Examiner doesn't point to any law, however, that

says a utility that is shared by a large class is somehow not a utility. If all of the class of expressed polynucleotides can be so used, then they all have utility. The issue is, once again, whether the claimed polynucleotide and encoded polypeptide has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of well-established" utilities PRESUPPOSES that many different inventions can have the exact same utility (if the Examiner's argument were correct, there could never be a well-established utility, because you could always find a generic group with the same utility!).

It is true that just about any expressed polynucleotide will have use as a toxicology control, but Appellants need not argue this for the purposes of this case. Appellants argue only that this particular claimed invention could be so used, and has provided, e.g., the First Bedilion Declaration, the Rockett Declaration, and the Iyer Declaration, to back this up. The point is not whether or not the claimed polynucleotide is, in any given toxicology test, differentially expressed. The point is that the invention provides a useful measuring stick regardless of whether there is or is not differential expression. That makes the invention useful today, in the real-world, for real purposes.

Appellants note that monitoring the expression of the claimed polynucleotide is a method of testing the toxicology of drug candidates during the drug development process. If the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide (or its encoded polypeptide) is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects that may limit its usefulness as a specific drug. Toxicology testing using microarrays reduces time needed for drug development by weeding out compounds which are not specific to the drug target. Learning this from an array in a gene expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

5. The Examiner on pages 8-9 of the Final Office Action asserts that the Appellants have made a misplaced analogy by comparing the claimed polynucleotides to a scale. The Examiner asserts that "it is the microarray that is analogous to a scale" while the claimed polynucleotide is analogous to objects which "might be weighted [*sic*] using that scale" which do not necessarily have patentable utility. With respect to the utility of the claimed polynucleotides in toxicology testing, the Examiner is wrong. The claimed polynucleotide may be used as a probe on the microarray. In toxicology testing as described above, the claimed polynucleotide is not the object of the research. The claimed polynucleotide is a research tool used to assess the toxicity of drug candidates which are specifically targeted to other polynucleotides. The other polynucleotides and the drug candidates are the objects of the research.

6. In addition, the use of an expressed polynucleotide as a control in a toxicology test is a specific and substantial utility. It is irrelevant whether this use "can be performed with any nucleic acid." (Final Office Action, page 8.) The Examiner implies that a utility is not substantial if the process carried out in applying that utility to an object can also be carried out on a different object. This is incorrect. The fact that one can apply a given process to a number of different objects does not mean that the process is not a specific utility when applied to a particular object. In the present case, a toxicology test can be carried out using any polynucleotide expressed in humans as a control, providing that the polynucleotide is not the target of the toxicology test. In carrying out such a test, a particular process can be applied using any expressed polynucleotide. However, each toxicology test using a given expressed polynucleotide as a control is a **distinct and unique** toxicology test because the results of the test are dependent on the identity of the expressed polynucleotide. A toxicology test using a given expressed polynucleotide is not interchangeable with a toxicology test using a different expressed polynucleotide, even if the particular process used in carrying out the toxicology tests are identical. The fact that the same series of steps can be used to carry out such toxicology tests does not prevent such tests from being a specific and substantial utility.

7. The Examiner argues that "even if this [the use in cDNA microarrays] were to be considered to be sufficient to meet the utility requirement under 35 USC 101, the

scope of the claims would not be commensurate with such use, as such use would apply only to the exact, naturally occurring sequence, and not to nucleic acids which vary from such by codon degeneracy (have different sequence, but encode the same protein) nor to nucleic acids 90% identical to the specifically disclosed sequence." (Final Office Action, page 5.) Appellants note that the Specification, along with what is well known in the art, teach that the claimed polynucleotides which comprise degenerate sequences to SEQ ID NO:4 are useful in toxicology testing in that they may be used in the production, either by recombinant or synthetic methods, of the polypeptide of SEQ ID NO:3. The claimed polynucleotide variants, as naturally-occurring sequences, or the polynucleotides encoding naturally-occurring polypeptide variants, have the same utility in toxicology testing as do SEQ ID NO:4 and the polynucleotide encoding SEQ ID NO:3. The polypeptide of SEQ ID NO:3 is useful as a control in methods that measure protein expression (e.g, ELISAs, 2-D PAGE gels) in cells, tissues, or organisms that have been treated with compounds during toxicology testing during drug development. (See, e.g., Rockett Declaration, ¶ 11-14.) The polypeptide of SEQ ID NO:3 may also be used in the production of antibodies also useful in methods that measure protein expression. (See the Specification, e.g, at page 29, line 30 through page 31, line 20, and page 37, line 25 through page 38, line 11. See also Rockett et al., Exhibit C of the Rockett Declaration; and Sandra Steiner and N. Leigh Anderson, Reference No. 13.

8. The Examiner argues that the use of the claimed polynucleotides as "highly specific" probes in cDNA microarray technology is not the same as the "specific utility" required by the Examiner to demonstrate utility. (Final Office Action, pages 3-4 and 7-8.) The Examiner contends that the use of the claimed polynucleotides in toxicology testing is a "non-specific utility" as it "can be attributed to any and all members of a class of compounds." (Final Office Action, pages 4 and 8.) Appellants direct the Examiner to the discussion under Issue One: Sections I and IV of this Brief, where the requirement for a utility that gives a "specific benefit" and not, as narrowly interpreted by the Examiner and the Training Materials, a "particular," "distinct," or "unique" utility.

9. Rockett and Lashkari references

The Final Office Action states that "[t]he Examiner notes that these references, e.g, Rockett et al and Lashkari et al have not been previously cited, nor have they been made of record by Applicants in any information disclosure statement." (Final Office Action, page 9.) Appellants first note that the Rockett et al. paper (Xenobiotica, 1999, 29:655-691) and the Lashkari et al. paper (Proc. Nat. Acad. Sci. U.S.A., 1997, 94:8945-8947) were submitted with the Response to Non-Final Office Action filed March 31, 2003, to provide evidence of the utility of the claimed invention in gene expression monitoring for toxicology testing.

Appellants second note first that the MPEP requires that the Examiner consider timely submitted references, regardless of whether or not they are included in an Information Disclosure Statement. MPEP in § 609, part III. C(3) "Documents Submitted As Part of Applicant's Reply to Office Action" that:

> Occasionally, documents are submitted and relied on by an applicant when replying to an Office action. These documents may be relied on by an applicant, for example, to show that an element recited in the claim is operative or that a term used in the claim has a recognized meaning in the art. Documents may be in any form but are typically in the form of an affidavit, declaration, patent, or printed publication.
>
> To the extent that a document is submitted as evidence directed to an issue of patentability raised in an Office action, and the evidence is timely presented, applicant need not satisfy the requirements of 37 CFR 1.97 and 37 CFR 1.98 in order to have the examiner consider the information contained in the document relied on by applicant. In other words, compliance with the information disclosure rules is not a threshold requirement to have information considered when submitted by applicant to support an argument being made in a reply to an Office action.

The Examiner is furthermore obliged to consider evidence provided by Appellants in support the patentability of the claims.

> Once a prima facie showing of no specific and substantial credible utility has been properly established, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by **providing evidence in the form of a declaration under 37 CFR 1.132 or a patent or a printed publication that rebuts the basis or logic of the prima facie showing. If the applicant responds to the prima facie rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the prima facie showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an**

> **asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility.** Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. (MPEP, § 2107 II. D., emphasis added.)

10. The Examiner alleged that the Rockett et al. (Exhibit C attached to the Rockett Declaration, cited previously in the Response filed March 31, 2003) and Lashkari et al. (Reference No. 12, previously also cited in the Response filed March 31, 2003) articles teach that use of a polynucleotide in microarrays is useful only for further characterization of the detected genes and probes themselves. (Final Office Action, pages 9-11.) The Examiner quoted the first sentence of the Rockett et al. abstract: "[a]n important feature of the work of many molecule [*sic*: molecular] biologists is identifying which genes are switched on and off in a cell under different environmental conditions of [*sic*: or] subsequent to xenobiotic challenge. **Such information has many uses, including the deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures**." (Final Office Action, page 10, emphasis given in Final Office Action.) The Examiner reads this sentence narrowly, suggesting that the Rockett et al. article teaches that the **only uses** for cDNA microarrays are for further characterization of the detected genes and probes. However, reading further than the first sentence of the Rockett et al. article's abstract, Appellants note that the authors expand the possible uses of differential gene expression analysis, stating that:

> Differential gene display provides a coherent platform for building libraries and microchip arrays of 'gene fingerprints' characteristic of known enzyme inducers and xenobiotic toxicants, which may be interrogated subsequently **for the identification and characterization of xenobiotics of unknown biological properties**. (Rockett et al., Exhibit C attached to the Rockett Declaration, cited previously in the Response filed March 31, 2003, abstract, page 655, emphasis added.)

Rockett et al. teach that "in the field of chemical-induced toxicity, it is now becoming increasingly obvious that most adverse reactions to drugs and chemicals are the result of multiple gene regulation, some of which are causal and some of which are casually-related to the toxicological phenomenon *per se*. This observation has led to an upsurge in interest in gene-

profiling technologies which differentiate between the control and toxin-treated gene pools in target tissues and is therefore, of value in rationalizing the molecule mechanisms of xenobiotic-induced toxicity. (Rockett et al., Exhibit C attached to the Rockett Declaration, cited previously in the Response filed March 31, 2003), page 656, italics in original.) Rockett et al. thus teach that microchip analyses are useful for, the "identification and characterization of xenobiotics of unknown biological properties," in addition to those uses in "deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures." The Examiner has ignored these teachings in the discussion in the Final Office Action.

Appellants further provide the Rockett Declaration as evidence of the utility of all expressed polynucleotide and polypeptide sequences, regardless of their biological function. Dr. Rockett states in his Declaration that:

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s . . . that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology. [Rockett Declaration, ¶ 18.]

The Examiner further alleges that the Lashkari et al. article (Reference No. 11) teaches that "sequences of unknown function or significance are used in such strategies [microarrays] **to learn more about the sequences themselves and the genes they represent**." (Final Office Action, page 11, emphasis in original.) The Examiner cites several lines from the first page of the Lashkari et al. article. Reading further into the article, Appellants note that Lashkari et al. teach broader uses for cDNA microarrays that the narrow reading adopted by the Examiner. For example, whole genome analysis is useful because it allows one to "analyze numerous genes under many conditions." (Lashkari et al., page 8946.) In addition, Lashkari et al. teach that data from genome projects will not only allow one "to gain a truly comprehensive understanding of gene function" but also "more broadly, of the entire genome." (Lashkari et al., page 8947.) Furthermore, such understanding "should come from the viewpoint of the integration of complex regulatory networks, the individual roles and interactions of thousands of functional gene products, and the effect of environmental changes on both gene regulatory networks and the roles of all gene products. The time has come to switch from the analysis of a single gene to the analysis of the whole genome." (Lashkari et al, page 8947.) Hence, the Lashkari et al. article

supports the utility of open reading frames (ORFs) in whole genome analysis by cDNA microarrays and in particular, for determining the "effect of environmental changes on gene regulatory networks and the roles of all gene products." (Lashkari et al., page 8947.)

The Examiner also disputes the evidence of the Afshari email (Reference No. 15, cited previously in the Response filed March 31, 2003), stating that "this is a utility which is nonspecific and applies to virtually every member of the general class of DNA." (Final Office Action, page 12.) As discussed supra in Section III.D.4. of this Brief, nothing in the law says that an invention must have a "unique" utility.

Appellants note that the Examiner does not comment on any of the other articles cited in either the Response filed March 31, 2003 or the First Bedilion Declaration which also support the utility of the claimed subject matter.

10. Applicants' Showing of Facts Overcomes The Examiner's Concern That Applicants' Invention Lacks "Specific Utility"

The Examiner alleges that "the use of the claimed nucleic acids in microarrays is not specific, as it could apply equally to any given nucleic acid." (Final Office Action, page 5.)

Appellants' submission of additional facts overcomes this concern. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotides as gene-specific probes ***depends upon*** specific properties of the polynucleotides, that is, their nucleic acid sequences.

"[E]ach probe on . . . [a "high density spotted microarray[]"], with careful design and sufficient length, and with sufficiently stringent hybridization and wash conditions, ***binds specifically*** and with minimal cross-hybridization, to the probe's cognate transcript" (Rockett Declaration, ¶ 10(i), emphasis added); "[e]ach gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation." (Iyer Declaration, ¶ 7[5], emphasis added.) Accordingly, "each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of this analytical device for gene expression profiling" (Rockett Declaration, ¶ 10(ii)); equally, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes

[5]See Iyer Declaration, footnote at ¶ 7 for a slightly more "nuanced" view.

detectable by the device, increasing the resolving power of the device." (Iyer Declaration, ¶ 7.)

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30-40 years.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p. 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed

invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category

of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

Issue Two: Enablement Rejection of Claims 3-7, 9-10, 12-13, and 49

The rejection set forth in the Final Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Issue Three: Enablement Rejection of Claims 3-4, 6-7, 9-10, and 12-13 with respect to with respect to naturally occurring sequences

The Examiner alleged that "even if utility were found for the nucleic acid of SEQ ID NO:4, the rejection of Claims 3-4, 6-7, 9-10, 12-13 under 35 USC 112, first paragraph would be retained because the urged utilities would apply only to the naturally occurring sequence and therefore that enablement of the urged uses of SEQ ID NO:4 is not commensurate in scope with Claims 3-4, 6-7, 9-10, 12-13." (Final Office Action, page 21.)

As discussed supra under Issue One, the Specification, along with what is well known in the art, teach that the claimed polynucleotides which comprise degenerate sequences to SEQ ID NO:4 are useful in toxicology testing in that they may be used in the production, either by recombinant or synthetic methods, of the polypeptide of SEQ ID NO:3. The polypeptide of SEQ ID NO:3 is useful as a control in methods that measure protein expression (e.g, ELISAs, 2-D PAGE gels) in cells, tissues, or organisms that have been treated with compounds during toxicology testing during drug development. The polypeptide of SEQ ID NO:3 may also be used in the production of antibodies also useful in methods that measure protein expression. (See the Specification, e.g, at page 29, line 30 through page 31, line 20, and page 37, line 25 through page 38, line 11. See also Rockett et al. Xenobiotica, 1999 29:655-691, page 686, Exhibit C attached to the Rockett Declaration, previously cited in the Response filed March 31, 2003; and Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations,

Toxicology Letters 112-13:467-471 (2000) (Reference No. 13, previously cited in the Response filed March 31, 2003).

The Examiner further maintained the rejection of Claims 3-4, 6-7, 9-10, and 12-13 on the basis that "the claims as written are not limited to naturally occurring sequences" and that "it is not recognized in the art to use non-naturally occurring sequences for any of the uses urged by Applicants." (Final Office Action, page 25.)

The claimed polynucleotide variants, claimed polynucleotide fragments, and claimed complementary sequences, as well as the claimed polynucleotides encoding SEQ ID NO:3, the claimed polynucleotides encoding polypeptide variants, and the claimed polynucleotides encoding polypeptide fragments contain products of expressed genes or their encoded polypeptides. Therefore, these polynucleotides are useful for the same purposes as the polynucleotides comprising the polynucleotide sequence of SEQ ID NO:4 and the polynucleotide encoding the polypeptide sequence of SEQ ID NO: 3. These utilities are described fully under the rejection under Issue One of this Brief, and in the First Bedilion Declaration, Second Bedilion Declaration, the Rockett Declaration, and the Iyer Declaration. In addition, the Specification discloses the use of complementary polynucleotides in antisense technology e.g., on page 8, line 25 through page 9, line 1, page 31, lines 22-29, page 32, lines 14-24, and page 52, lines 1-10. This satisfies the "how to use" requirement of 35 U.S.C. § 112, first paragraph.

Issue Four: Enablement Rejection of Claims 3-7 and 9-10, with respect to expressed sequences and expressed polypeptides

Claims 3-7 and 9-10 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification "while being enabling for a polynucleotide comprising SEQ ID NO:4, does not reasonably provide enablement for a polynucleotide encoding SEQ ID NO:3 or a method of making SEQ ID NO:3." (Office Action mailed December 31, 2002, page 9). The Examiner maintained the enablement rejection of Claims 3-7 and 9-10 on the basis that "it is unknown if the polynucleotide of SEQ ID NO:4 is an expressed sequence" and even if the polynucleotide of SEQ ID NO:4 is expressed, "it is known in the art that correspondence of mRNA levels and protein levels is not predictable." (Final Office Action, page 21-25.)

The Office Action asserts that "[b]ecause SEQ ID NO:4 is simply a polynucleotide

fragment, it is not possible to determining [*sic*] what the ATG start site of any protein might be and it cannot be determined if the sequence would be in-frame to encode any protein" (Office Action mailed December 31, 2002, page 10). These assertions ignore the disclosure of the specification. For example, the exact amino acid sequence of the polypeptide encoded by the SEQ ID NO:4 polynucleotide is explicitly set out as SEQ ID NO:3 in the Sequence Listing, and is also disclosed in Figures 2A, 2B, 2C, 2D, and 2E. In addition, Figures 2A, 2B, 2C, 2D, 2D, and 2E delineate the precise ATG start site and translation frame for the translation of the SEQ ID NO:3 polypeptide encoded by the SEQ ID NO:4 polynucleotide. Based on the disclosure in the specification, there is no need for one of skill in the art to "determine what the ATG start site" might be, or "if the sequence would be in-frame to encode any protein," because such determinations have already been provided by the patent application.

I. The Specification and what is well known in the art provide adequate evidence that SEQ ID NO:4 is an expressed polynucleotide sequence

The Examiner further rejected the claimed invention on the basis that the method of isolation, assembly of multiple overlapping sequences of transcribed ESTs, is not credible evidence of the existence of the full-length cDNA. In particular, the Examiner alleged that "it is unknown if the polynucleotide of SEQ ID NO:4 is an expressed sequence" because "SEQ ID NO:4 is a consensus sequence product of six clones derived from overlapping and/or extended nucleic acid sequences," "SEQ ID NO:4 is not a polynucleotide that has been isolated from a living cell, it is a DNA fragment produced with recombinant techniques." (Final Office Action, page 22.) The Examiner also alleges that "it is unknown whether the sequence is found in nature or is expressed in nature, or whether if it is expressed in nature, whether it encodes the expressed polypeptide of SEQ ID NO:3 in nature." (Final Office Action, page 22.)

Methods of deducing a DNA sequence by overlapping clones well-known in art. For example, Ausubel teaches that:

> The practical limit on the amount of information that can be obtained from a set of sequencing reactions is the resolution of the sequencing gel. . . Current technology allows ~300 nucleotides of sequence information to be reliably obtained in one set of sequencing reactions, although more information (up to 500 nucleotides) is often obtained. Thus, is the region of DNA to be sequenced is <300 nucleotides, a single cloning into the appropriate vector is all that is usually necessary to produce

> a recombinant molecule that can be easily sequenced.
> For a larger region of DNA, it is generally necessary to break a large fragment into smaller ones that are then individually sequenced. This can be done in a random or an ordered fashion. (Ausubel, page 7-1.)
>
> **********
>
> With increasing worldwide interest in genome sequencing projects, sequence assembly packages now provide very effective automatic DNA sequence assembly, connecting shorter pieces of DNA to build the longest continuous sequence possible. Once that sequences to be assembled are identified, they are compared, overlaps identified, and contiguous sequences (contigs) constructed. (Ausubel, page 7-52.)

F.M. Ausubel, et al., (1997) Short Protocols in Molecular Biology, Third Edition, John Wiley & Sons, New York, NY (cited pages included as Reference No. 16).

Moreover, the Examiner has provided neither evidence nor sound scientific reasoning to explain why one of skill in the art would doubt that SEQ ID NO:4 is an expressed polynucleotide.

II. The existence of a mRNA is reasonable evidence of an expressed polypeptide

The Final Office Action maintained the enablement rejection on the basis that "[o]ne cannot extrapolate the teaching of the specification to the scope of the claims because there is no teaching of whether any protein product is actually produced **in vivo**" (Office Action mailed December 31, 2002, page 10, emphasis in original) and that "the nexus of mRNA level to protein level in a cell is unpredictable," citing examples of post-transcriptional regulation (Final Office Action, page 23.) Appellants submit that the Specification and what is well known in the art provide adequate evidence that the SEQ ID NO:3 polypeptide is expressed.

The question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:3 expression, but rather, whether one skilled in the art would have a reasonable expectation that the existence of the SEQ ID NO:4 polynucleotide would predict the production of the SEQ ID NO:3 polypeptide. In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:3 were controlled predominantly in a post-transcriptional manner,

thereby dismissing the significance of mRNA levels.

The Examiner disputes the value of the Lewin reference cited in the Response filed March 31, 2003, stating that Lewin teaches that "the production of RNA cannot inevitably be equated with production of protein." (Final Office Action, page 22.) Appellants note that the Examiner quoted only a portion of the cited Lewin sentence, which reads in its entirety,

> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that *the overwhelming majority of regulatory events occur at the initiation of transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation* [pages 847-848, emphasis added].

The Examiner asserts that "the nexus of mRNA level to protein level in a cell is unpredictable" and that "evidence abounds that this is known in the art" (Final Office Action, page 23). Appellants respectfully dispute the Examiner's assertion. While the Examiner presented several reports from the literature in support of this assertion, a thorough reading of these reports revealed that in many cases, although no quantitative correlation was found between mRNA and protein levels, a qualitative correlation existed. Indeed many of the Examiner's cited references support Appellants' position that mRNA levels are usually a good indicator of protein levels.

For example, the Examiner states, "Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and protein level." (Final Office Action, page 23.) Just prior to the statement the Examiner is paraphrasing, Zimmer states that "the distribution of S100 mRNAs parall[el]ed the protein distribution in different muscle types," suggesting that while there was no mathematical correlation between mRNA and protein, there was a qualitative correlation. (Zimmer, page 325.) That is, in most cases, protein is present when the corresponding mRNA is detected, thus, detection of mRNA would accurately reflect the presence of the encoded protein. In another example the Examiner asserts that "Eriksson et al. (Diabetologia, 1992, vol. 20, pp. 325-337) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby." (Final Office Action, page 23.) The data presented by Eriksson and colleagues show that in *every* group tested, protein is present when mRNA is detected (e.g.,

Eriksson et al., Table 3, page 145). Indeed this is another example of a qualitative relationship between mRNA levels and levels of the encoded protein. In yet another example, the Examiner cites a study by Hell et al. comparing the expression of the bcl-2 oncogene in cells from patients with various types of Hodgkin's disease (Laboratory Investigation 73:492-6, 1995). The Examiner states, "Hell et al. teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells" (Final Office Action, page 23). However, the data show that in each of the 16 cases presented, the bcl-2 protein was present when the corresponding mRNA was detected. The authors subsequently argue "[i]n the follicle mantle zone...with few lymphocytes that demonstrated a positive signal for bcl-2 mRNA using ISH [*in situ* hybridization] and high protein expression levels, indicating a posttranscriptional regulation of *bcl-2* protein expression." (Hell et al., page 494.) Even in a case such as this one where regulation appears to be post-transcriptional, there still remains a qualitative correlation between the presence of mRNA and the presence of the encoded protein. Similarly, in another report cited by the Examiner, a qualitative correlation between the presence of mRNA and the encoded protein for the NRF-2 α and β subunits is observed, although their regulation is purportedly post-transcriptional (Vallejo et al., Biochimie 82:411-21, 2000). This point is made again in the study by Powell et al. (Pharmacogenetics 8:411-21, 1998) cited by the Examiner. As stated by the Examiner, "Powell et al. ... teach that mRNA levels for cytochrome P450 [2]E1 did not correlate with the level of corresponding protein and conclude that the regulation of said protein is highly complex." (Final Office Action, page 23.) Indeed Powell et al. state further that "CYP2E1 also appears to be unique among the P450 isoforms in that it is regulated the pre-transcriptional, transcriptional, pre-translational, translational and post-translational levels." (Powell, page 417.) Even given this complicated mechanism of regulation of expression, the data in this report show that in each sample tested, CYP2E1 protein was found when the corresponding mRNA was detected. A qualitative relationship can also be seen between OATP mRNA and protein in the study by Guo et al. (Journal of Pharmacology and Experimental Therapeutics 300:206-12, 2002); that is, when mRNA is detected, the corresponding protein is also present.

In another example, the Examiner states that Brennan et al. (Journal of Autoimmunity 2(suppl.):177-86, 1989) "teach that high levels of the mRNA for TNFα were produced in

synovial cells, but that levels of the TNFα protein were undetectable." (Final Office Action, page 22.) A careful reading of this paper shows that TNFα was not detected *above the detection limit* of the immunoassay the authors employed. In fact, the authors state in several places that "since the relevant protein (>50pg/mL) was not detected *more sensitive assays are clearly needed* to explore this further." (Brennan et al., page 182, emphasis added.) The authors state further that "[t]he assay used detects 50 pg/mL (5 U/mL) and as such is not as sensitive as bioassays which can detect (0.1 U/mL)" and conclude that "it is conceivable that low but significant levels of protein are produced." (Brennan et al., page 185.) Furthermore, the assays used by the authors measured secreted TGFα rather than total TGFα (i.e., both secreted and *non-secreted* protein). For at least these reasons, one cannot make any solid conclusion about the relationship of mRNA to protein in this case because the protein levels may not have been assayed appropriately.

In another example, the Examiner states that Carrere et al. (Gut 44:545:51, 1999) "teach an absence of correlation between protein and mRNA levels for the Reg protein." (Final Office Action, page 23.) Appellants respectfully submit that the Examiner has erred in the interpretation of this paper. The authors state in the "Results" section of the abstract, "[n]o correlation was found between the levels of Reg protein and trypsin (ogen) (or lipase) in CF, nor in control sera or normal pancreatic juice. Molecular gene expression of the corresponding proteins investigated in pancreatic tissues showed an absence of correlation between the mRNA levels." (Carrere et al., page 545.) The purpose of this study was to look for a correlation between the concentration of Reg protein in serum and the concentration of other serum proteins also secreted by the pancreas (e.g., trypsin and lipase) in populations of patients with or without pancreatic disease. The paper compared the protein levels of these various pancreatic proteins. The paper also compared the levels of the mRNA encoding the Reg protein with the levels of the mRNAs encoding the other pancreatic proteins. The "absence of correlation" to which the authors refer is between the mRNA level of Reg with the mRNA levels of the other pancreatic proteins, *not* between protein levels and mRNA levels of an individual protein/gene. Indeed the veracity of this interpretation is evident through an even cursory review of the data; all comparisons are protein to protein or mRNA to mRNA *not* protein to its corresponding mRNA. Furthermore, there is no measure of Reg protein in pancreatic tissue (whereas mRNA levels *were* measured in pancreatic tissue); protein levels were only measured in serum or pancreatic juice

(i.e., the external secretion of the pancreas). Therefore, one could not even reach the Examiner's conclusion, irrespective of the authors' conclusions, by looking at the data presented because the level of the Reg protein *in pancreatic tissue* was not determined, that is, Reg protein and mRNA levels were measured in *different* biological samples.

In another example, the Examiner cites a study by Jang et al. (Clinical and Experimental Metastasis 15:469-83, 1997) and states that the authors "teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes." (Final Office Action, page 24.) The authors studied the expression of 6 metastasis-associated genes in cells cultured under conditions of growth stress to determine if changes in the expression of any of these genes could explain an increase in metastatic ability. The authors report essentially negative data, that is, no correlation between changes in mRNA levels of the 6 genes and the observed increase in metastatic ability. A comparison between protein and mRNA levels cannot be made in this instance because they measured mRNA but *not* protein levels of these genes. The point of the study was to determine if a change in expression, as measured by mRNA levels, was responsible for the increased metastatic ability. Upon a finding of no correlation between the two, the authors suggested that a study of protein levels might yield data supporting their hypothesis. It should not be surprising that the authors would suggest looking at protein levels since those determinations were not made and there may indeed be a correlation between one of these proteins and metastatic ability. The fact that they cannot anticipate the protein levels from the mRNA levels does not exclude the possibility that a relationship, whether quantitative or qualitative, does indeed exist between mRNA and corresponding protein of the genes studied.

Appellants respectfully reiterate the assertion that mRNA levels are usually a good indicator of protein levels. This suggests that the regulation of genes is at the level of transcription. While there are examples in the literature of genes that are regulated post-transcriptionally, the authoritative text in the field of molecular biology (*The Molecular Biology of the Cell*) as well as a wealth of data in the literature indicate that the *predominant* level of control of gene expression is at transcription. For example, in discussing the complicated process of gene expression, Alberts et al. state,

There are many steps in the pathway leading from DNA to protein, and all

> of them can in principle be regulated. Thus a cell can control the proteins it makes by (1) controlling when and how often a given gene is transcribed (transcriptional control), (2) controlling how the primary RNA transcript is spliced or otherwise processed (RNA processing control), (3) selecting which completed mRNAs in the cell nucleus are exported to the cytoplasm (RNA transport control), (4) selecting which mRNAs in the cytoplasm are translated by ribosomes (translational control), (5) selectively destabilizing certain mRNA molecules in the cytoplasm (mRNA degradation control), or (6) selectively activating, inactivating or compartmentalizing specific protein molecules after they have been made (protein activity control).
>
> **For most genes transcriptional controls are paramount.**
>
> * * * * *
>
> Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control."
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> (*The Molecular Biology of the Cell*, Alberts B. et al., editors, Garland Publishing, Inc., 1994, 3rd Edition, Reference No. 17 pages 403-404, emphasis added.)

Even in discussing posttranscriptional controls, Alberts et al. state that, "[a]lthough controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." (Alberts et al., Reference No. 17, page 453.) Indeed Alberts et al. goes on to describe several examples of genes exhibiting posttranscriptional control. However, the fact that there are examples of genes that are regulated by posttranscriptional controls, does not detract from the observation that the *preponderance* of genes are regulated at the level of transcription. This, therefore supports Appellants' assertion that mRNA levels are *usually* a good indicator of protein levels.

Furthermore, there is an abundance of data in the literature in support of Appellants' assertion and in corroboration with the statements set forth by Alberts et al. Appellants present reports from the literature published before the April 29, 1998 priority date of the instant application, which show, at a minimum, a qualitative correlation between mRNA and protein or, in many cases, a quantitative correlation between the two. For example, Nooter et al. (Ann. Oncol. 7:75-81, 1996; Reference No. 18) report a quantitative correlation between mRNA levels and the encoded protein for multi-drug resistance-associated protein (MRP). The authors report "MRP expression, as estimated by immunohistochemistry, correlated with the MRP mRNA

levels quantitated by RNase protection assay." (Nooter et al., page 75.) In another example, Meyer-Siegler et al. (Carcinogenesis 13:2127-32, 1992; Reference No. 19) report that the "increase in GAPDH/UDG gene expression was identical to that observed for UDG enzyme activity" and conclude that "a correlation existed between the transcription of this gene and the level of uracil DNA glycosylase [UDG] enzyme activity." (Meyer-Siegler et al., page 2127.) In yet another example, Shinohara et al. (Biochim. Biophys. Acta 1368:129-36, 1998; Reference No. 20) state that "[a] good correlation was found between the reported HK [hexokinase] activities and the total amounts of transcripts encoding all HK isozymes in various tissues" and conclude that "the HK activities in tissues can be estimated from the total amount of transcripts encoding HK isozymes." (Shinohara et al., page 129.) In still another example, Del Carratore et al. (Carcinogenesis 13:2175-7, 1992; Reference No. 21) report that "[t]he increased level found for this transcript [CYP51] in cells treated with ethanol, 20% glucose, phenobarbital or 5-methoxypsoralen correlates with the levels of induction in cytochrome P450 enzymatic activity measured in cells grown under the same conditions." (Del Carratore et al., page 2175.) The authors conclude that their data indicate that "[i]nduction of cytochrome P450 by ethanol, 20% glucose, phenobarbital or 5-methoxypsoralen appears to be regulated at the transcriptional level." (Del Carratore et al., page 2176.) In another example, Belluardo et al. (Neuroscience 83:723-40, 1998; Reference No. 22) report, "acute intermittent (-)nicotine treatment...lead to a substantial and dose-related ... up-regulation of fibroblast growth factor-2 messenger RNA levels" and that "[t]he change of fibroblast growth factor-2 messenger RNA levels was associated with increased fibroblast growth factor-2 immunoreactivity mainly localized to nerve cells." (Belluardo et al., page 723.)

Moreover, a number of recent studies have been published in the literature in support of Appellants' assertion. For example, in a study of TNFα expression in human monocytes and THP-1 cells upon stimulation with *Pseudomonas aeruginosa* extracellular slime glycolipoprotein (GLP), Lagoumintzis et al. (Infect. Immun. 71:4614-22, 2003; Reference No. 23) report that the "[r]egulation of TNFα production induced by *P. aeruginosa* GLP occurs at the transcriptional level." (Lagoumintzis et al., page 4615.) In another example, in a study of HER2/neu expression in synovial sarcoma, Nuciforo et al. (Hum. Pathol., 34:639-45, 2003; Reference No. 24) report "a strong, statistically significant association was present between protein expression, for both

membrane and cytoplasmic staining, and HER2/neu mRNA levels." (Nuciforo et al., page 642.) In another example, Vandebriel et al. (Toxicology 188:1-13, 2003; Reference No. 25) report "a good qualitative correlation between mRNA expression and production of IFN-γ and IL-4." (Vandebriel et al., page 1). In yet another example, Wang et al. (NeuroReport 14:817-23, 2003; Reference No. 26) found that "sustained loud sound (3 days at 90 dB SPL) produced a significant increase in $P2X_2R$ protein expression in the regions [rat organ of Corti and spiral ganglion] shown to have $P2X_2R$ transcript up-regulation." (Wang et al., page 820.)

Furthermore, the use of DNA microarrays is emerging as an important methodology in the study of the expression of large numbers of genes simultaneously. In this technique mRNA levels and changes therein (as a result of disease, chemical, or therapeutic perturbations, for example) are measured. mRNA levels are measured as a surrogate for protein because it is the protein which in most cases effects any change in cellular phenotype. In a review article by Clarke et al. (Biochemical Pharmacology 62:1311-1336, 200; Reference No. 27), the authors point out that although in the *ideal* scenario, protein and mRNA would be measured side-by-side in the same experiment, the proteomic technologies tend to be "lower throughput, more technologically challenging, and less readily compatible with routine material from clinical studies." (Clarke et al., page 1314) On the other hand, with respect to RNA-based microarrays, the authors state "[c]urrent RNA-based approaches to assess gene expression have been demonstrated to be both robust and reproducible." (Clarke et al., page 1314) While the authors note that there are examples in the literature of *selected* proteins whose protein and mRNA levels do not correlate, they assert that "[c]hanges in the molecular phenotype of the cell should be accurately reflected by its transcriptional profile, and the evaluation of gene expression by measuring mRNA should provide a molecular signature of the state of the activity of the cell and by extension the activity of the proteins that regulate that state." (Clarke et al., page 1314.) This supports Appellants' assertion that mRNA levels are a good indicator of protein *in most cases*; absent specific experiments to the contrary on a particular protein of interest, it is reasonable to assume that mRNA levels will adequately reflect protein levels.

Furthermore, based on the what is known in the art, one skilled in the art would have a reasonable expectation that the existence of the SEQ ID NO:4 polynucleotide would predict the

production of the SEQ ID NO:3 polypeptide.

Issue Five: Enablement Rejection of Claims 3-4, 6-7, 9-10, and 12-13 with respect to polynucleotides encoding polypeptide variants, polynucleotides encoding SEQ ID NO:3, polynucleotides encoding a polypeptide fragment, polynucleotide variants, and complementary polynucleotides

The Examiner maintained the rejection from the Office Action mailed December 31, 2002 which stated that "the specification, while being enabling for a polynucleotide comprising SEQ ID NO:4 and the complete complement thereof does not reasonably provide enablement for polynucleotides encoding naturally occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO: 3, encoding polypeptides having the amino acid sequence of SEQ ID NO:3, encoding a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3 having . . . immunogenic activity, naturally occurring polynucleotides having at least 90% identity to SEQ ID NO:4, polynucleotides complementary to SEQ ID NO:4 or said naturally occurring polynucleotide with at least 90% identity to SEQ ID NO:4 or fragments of SEQ ID NO:4." (Office Action mailed December 31, 2002, page 11.) The Examiner states that "[t]he specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with these claims." (Office Action mailed December 31, 2002, pages 11-12.)

The Examiner in the December 31, 2002 Office Action further stated that "**[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention** commensurate in scope with the claims since **the specification gives no guidance on or exemplification of how to make/use the polynucleotides** that encode the broadly claimed polypeptides for the reasons disclosed above drawn to the Bowie et al, Lazar et al, and Burgess et al references." (Office Action mailed December 31, 2002, page 13, emphasis added) In response to this rejection, Appellants in the Response filed March 31, 2003 presented arguments as to why the specification, along with what is known in the art, enabled one of skill to make and use the invention. However, in the Final Office Action, the Examiner stated that "Applicant argues on page 30-32 that the making of the claimed invention is enabled. The argument is noted but has

not been considered because **the scope rejection of Claims 3-4, 6-7, 9-10 and 12-13 under 35 USC 114 first paragraph imposed on pages 11-15 of the Office Action is not drawn to how to make the invention, but rather how to use the claimed invention**." (Final Office Action, page 25, emphasis added.)

In reviewing the rejections as listed in both the Office Action mailed December 31, 2002 and the in the Final Office Action, Appellants are unsure of whether there is an enablement rejection on the basis of how to make the invention. Hence, Appellants present herein arguments that the making of the claimed invention is enabled.

The claimed polynucleotides are enabled, i.e., they are supported by the Specification and what is well known in the art.

I. How to make

SEQ ID NO:3 and SEQ ID NO:4 are specifically disclosed in the application (see, for example, pages 60-61 of the Sequence Listing). Variants of SEQ ID NO:3 and SEQ ID NO:4 are described, for example, on page 3, lines 9-11, page 3, line 29 through page 4, line 6, page 15, line 27 through page 16, line 5, and page 18, lines 1-4 and 11-21. Incyte clones in which the nucleic acids encoding the human PAWES-2 were first identified and libraries from which those clones were isolated are disclosed, for example, on page 17, lines 10-15 and page 44, lines 1-2. Chemical and structural features of PAWES-2 are disclosed, for example, on page 17, lines 16-24. Examples of SEQ ID NO:3 and SEQ ID NO:4 fragments are given on page 17, lines 24-26.

The Examiner alleged that "even a single amino acid substitution or what appears to be an inconsequential modification will often dramatically affect the biological activity and characteristic of a protein," and "the specification has not shown that variant polynucleotides or polynucleotides encoding polypeptides produced by variants of polynucleotides encoding SEQ ID NO:3 or polynucleotides comprising fragments of SEQ ID NO:4 are capable of functioning as that which is suggested." (Office Action mailed December 31, 2002, pages 12-13.) However, Applicants submit that the polypeptide variant sequences and polynucleotide variant sequences are described by their being "naturally occurring" and by their percentage sequence identity with SEQ ID NO:3 and SEQ ID NO:4 and not by biological activity or biological "function." The choice of amino acids or nucleotides to alter is made by nature. "Naturally occurring"

polypeptide variant sequences and polynucleotide variant sequences occur in nature; they are not created exclusively in a laboratory. The Specification teaches how to find polynucleotide variants (e.g., page 38, line 27 through page 39, line 1) which can then be expressed to make polypeptide variants and how to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4" scope and whether a given naturally occurring amino acid sequence falls within the "at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3" scope (e.g., page 11, lines 5-21 and page 45, lines 2-19). In addition, determination of percent identity is well known in the art.

For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application. See, e.g., page 19, lines 17-21; page 20, lines 1-28; page 38, line 12 to page 39, line 9; and Example VI at pages 50, line 23 through page 51, line 8. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:3, or vast numbers of polynucleotides based on the polynucleotide sequence of SEQ ID NO:4. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides of SEQ ID NO:4 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:3 recited by the present claims using conventional techniques of recombinant protein production. By extension, one of skill in art could make fragments of naturally occurring polynucleotides at least 90% identical to SEQ ID NO:4, and could use such fragments, for example, as hybridization probes to detect full-length naturally occurring polynucleotides at least 90% identical to SEQ ID NO:4.

The making of the claimed polynucleotide by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 19, lines 11-16, page 21, lines 9-14, and page 21, lines 23-26. The making of the claimed polynucleotide comprising a complementary

sequence is disclosed in the Specification at, e.g., page 31, lines 24-29, page 32, lines 13-24, page 33, lines 9-17, and page 52, lines 1-10.

Applicants submit that the specification fully enables the making of the claimed polynucleotide encoding an immunogenic fragment of SEQ ID NO:3. The polypeptide sequence of SEQ ID NO:3 is provided in the Sequence Listing. Preparation of immunogenic fragments is described in the Specification, e.g., at page 30, lines 8-14 and page 55, lines 8-17.

The ability of a given fragment to induce a specific immune response in animals or cells, or to bind with specific antibodies (See Specification at, e.g., page 9, lines 3-6, and page 55, lines 5-21) are tests for whether the fragment is "immunogenic." The tests of fragments by these methods do not require undue experimentation; the specification provides a test for antibody binding e.g., at page 43, lines 13-16.

This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

II. How to Use

The claimed polynucleotide variants, claimed polynucleotide fragments, and claimed complementary sequences, as well as the claimed polynucleotides encoding SEQ ID NO:3, the claimed polynucleotides encoding polypeptide variants, and the claimed polynucleotides encoding polypeptide fragments are products of expressed genes or encode expressed polypeptides. Therefore, these polynucleotides are useful for the same purposes as the polynucleotides comprising the polynucleotide sequence of SEQ ID NO:4 and the polynucleotide encoding the polypeptide sequence of SEQ ID NO: 3. These utilities are described fully under the rejection under Issue One of this Brief, and in the First Bedilion Declaration, Second Bedilion Declaration, the Rockett Declaration, and the Iyer Declaration. In addition, the Specification discloses the use of complementary polynucleotides in antisense technology e.g., on page 8, line 25 through page 9, line 1, page 31, lines 22-29, page 32, lines 14-24, and page 52, lines 1-10. This satisfies the "how to use" requirement of 35 U.S.C. § 112, first paragraph.

The Examiner further cited Bowie et al., Burgess et al., and Lazar et al. in support of the argument that the claimed variant polynucleotides and recited variant polypeptides may have different biological functions than SEQ ID NO:4 and SEQ ID NO:3.

However, these documents do not support the enablement rejection as the Specification,

along with what is well known to one of skill in the art, enable the use of the claimed polynucleotides in toxicology testing by virtue of their being expressed polynucleotides, or by virtue of encoding expressed polypeptides, regardless of their biological function. The Examiner has confused use with biological function.

The Office Action mailed December 31, 2002 asserts that "the specification has not shown that [the claimed polynucleotides] are capable of functioning as that which is suggested" because "even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein" (Office Action mailed December 31, 2002, pages 12-13). This is incorrect. One of skill in the art would reasonably conclude that the claimed polynucleotides encode polypeptide variants having the functions of the polypeptide of SEQ ID NO:3. However, in a recent Federal Circuit decision (Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corporation and Schering Corporation; CAFC 02-1026, -1027, February 21, 2003), the Court stated that "the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence."

While it may be true that some amino acid substitutions can dramatically affect biological activity of a protein, the recited polypeptide variants encoded by the **claimed** polynucleotides have naturally occurring amino acid sequences, and natural selection acts to conserve protein function. For example, as taught by Bowie et al. (Science, 1990, 247:1306-1310; cited by the Office Action mailed December 31, 2002 Office Action and the Final Office Action), proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences between the SEQ ID NO:3 polypeptide and the recited polypeptide variants comprising naturally occurring amino acid sequences at least 90% identical to SEQ ID NO:3 are likely to occur at positions of minimal functional importance, while residues conserved are likely those that are important for protein function.

The Office Action mailed December 31, 2002 and the Final Office Action cite Bowie et al. (*supra*), Burgess et al. (J. Cell Biol., 1990, 111:2129-2138), and Lazar et al. (Mol. Cell Biol., 1998, 8:1247-1252) in support of the Patent Office's assertions. The Office Action mailed December 31, 2002 have applied a limited subset of the results taught by these references, and have refused to consider the teachings of these references as a whole. Based on this limited analysis, the Office Action mailed December 31, 2002 has concluded that "the specification has not shown that [the claimed polynucleotides] are capable of functioning as that which is suggested" (Office Action, pages 12-13).

Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding, and show that this mutation is unable to completely eliminate the biological activity of the wild-type HBGF-1 protein (see, e.g., Burgess et al., abstract). Therefore, one of skill in the art would still be able to use these altered polypeptides **in the exact same manner as one would use the nonaltered polypeptides**, even though the results would not be exactly the same as if the nonaltered polypeptides were used.

Similarly, Lazar et al. discloses the results of making seven different mutations in TGF-alpha at either residue 47 or 48 (e.g., at Table 1 on page 1250). Only one of these mutations, the mutation of leucine 48 to alanine, results in a complete loss of function. The other six mutations result in polypeptide variants that can be used in exactly the same way as the wild-type polypeptide can be used, albeit the results of such use would not be identical. Residue 48 is one of 11 amino acids (from a total of 50) which are conserved among members of the EGF-like growth factors (Figure 1 of Lazar et al., page 1248). Thus, it is significant that only one out of the three mutations made at this conserved amino acid residue results in complete loss of TGF-alpha activity (Table 1 of Lazar et al., page 1250). Considering the teachings of Lazar et al. as a whole, one of skill in the art would recognize that polypeptide variants would more likely than not retain the function of the wild-type polypeptide.

One of skill in the art, considering the references cited by the Office Action mailed December 31, 2002 and the Final Office Action as a whole, would understand how to use the recited variants of SEQ ID NO:3; even if the results achieved from using the recited variants were not equivalent to the results achieved from using the SEQ ID NO:3 polypeptide, one of skill in the art would still be able to achieve **some** level of results by using the recited variants in the

same manner as the SEQ ID NO:3 polypeptide. This is all that is required to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

With respect to the claimed fragments, one of skill in the art could make and use the claimed polynucleotide fragments, and the claimed polynucleotides encoding the recited polypeptide fragments, without undue experimentation, based on the specification and the state of the art at the time the application was filed. For example, one of skill in the art would know how to use the claimed polynucleotide fragments, and polynucleotides encoding the recited polypeptide fragments, as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:4 (Specification, e.g., page 19, lines 17-21; page 20, lines 6-28, page 38, line 12 to page 39, line 9; and Example VI at pages 50-51). As discussed above, it is not necessary for a polynucleotide fragment to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide fragment without undue experimentation.

Furthermore, the Office Action mailed December 31, 2002 states that "it would not be possible to determine with any predictability whether, for example, the antibodies produced from the claimed immunogenic fragment that could be derived from SEQ ID NO:3 will actually bind to SEQ ID NO:3" (Office Action, page 13). The specification defines immunologically active (a synonym for immunogenic) as "the capability of the natural, recombinant, or synthetic PAWES, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies." (e.g., at page 9, lines 4-6). Therefore, the recited immunogenic fragments, encoded by the claimed polynucleotides, are those fragments which can induce a specific immune response and bind with specific antibodies. One of skill in the art would know how to make polynucleotides encoding immunogenic fragments, and could use the claimed polynucleotides, for example, as hybridization and/or PCR probes to detect polynucleotides encoding the SEQ ID NO:3 polypeptide. One of skill in the art would also know how to use such polynucleotides, for example, in toxicology testing for drug discovery.

The disclosure in the specification regarding the production of antibodies is broad. For example, the specification at page 29, lines 23-25 discloses that "purified PAWES may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind PAWES. Antibodies to PAWES may also be generated using methods that are well known in the art." As the Examiner recognizes, it is well known in the art that "it is

possible to produce antibodies to almost any part of an antigen" (Office Action mailed December 31, 2002, page 13). Thus, there is no doubt that it would be routine for one of skill in the art to produce antibodies using fragments of PAWES-2 (SEQ ID NO:3).

The specification also discloses methods of screening antibodies for specific immunogenic properties, for example, at page 31, lines 13-20:

> Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between PAWES and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering PAWES epitopes is preferred, but a competitive binding assay may also be employed. (Maddox, supra.)

Therefore, based on the disclosure in the specification and the state of the art at the time the application was filed, it would have been routine for one of skill in the art to make antibodies using fragments of SEQ ID NO:3 and to determine which of the resulting antibodies could bind to PAWES-2, without undue experimentation.

The Office Action mailed December 31, 2002 cites references that demonstrate that it may be difficult to predict which portions of intact proteins constitute epitopic regions which could provoke an immune response. (Holmes, Exp. Opin. Invest. Drugs, 2001, 10(3):511-519; Roitt et al., Immunology, 4th ed., Mosby, London (1998). However, it is not necessary to accurately predict epitopes in order to make and/or use the recited immunogenic fragments of SEQ ID NO:3. The cited references have no bearing on the ability of a skilled artisan to make antibodies to PAWES-2 fragments, and screen these antibodies for their ability to bind PAWES-2, without undue experimentation.

For at least the above reasons, the specification enables one of skill in the art to make and use the recited immunogenic fragments of SEQ ID NO:3.

Furthermore, the Office Action mailed December 31, 2002 asserts that "it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims **would not** share either structural or functional properties with polynucleotides that encode SEQ ID NO:3 or encode proteins that share either structural or functional properties with SEQ ID NO:3." (Office Action, page 15; emphasis in original). Applicants respectfully submit

that all of the claimed complementary polynucleotides would share **structural** properties with polynucleotides of SEQ ID NO:4. Thus, one of skill in the art could make and use the claimed complementary polynucleotides, without undue experimentation, based on the specification and the state of the art at the time the application was filed. For example, one of skill in the art would know how to use the claimed complementary polynucleotides as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:4 (Specification, e.g., page 19, lines 17-21, page 20, lines 6-28, page 38, line 12 to page 39, line 9, and Example VI at pages 50-51). As discussed above, it is not necessary for a complementary polynucleotide to share "functional properties with polynucleotides that encode SEQ ID NO:3" for one of skill in the art to be able to use that complementary polynucleotide without undue experimentation. One of skill in the art would also know how to use such polynucleotides, for example, in toxicology testing for drug discovery.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Final Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited polynucleotides.

Issue Six: Written Description Rejection of Claims 3-4, 6-7, 9-10, and 12-13

The Examiner maintained the written description rejection of Claims 3-4, 6-7, 9-10, and

12-13 alleging that "[t]he written description in this case only sets forth SEQ ID NO:4 and the complete complement thereof and therefore the written description is not commensurate in scope with the claims drawn to polynucleotides encoding naturally occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO:3, encoding polypeptides having the amino acid sequence of SEQ ID NO:3, . . . , encoding immunogenic fragments of SEQ ID NO:3, naturally occurring polynucleotides having at least 90% identity to SEQ ID NO:4, polynucleotides complementary to SEQ ID NO:4 or said naturally occurring polynucleotide with at least 90% identity to SEQ ID NO:4." (Office Action mailed December 31, 2002, pages 15-16.)

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described** in the specification, then the adequate description requirement is met. (emphasis added, citations omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:3 and SEQ ID NO:4 are specifically disclosed in the application (see, for example, pages 60-61 of the Sequence Listing). Variants of SEQ ID NO:3 are described, for example, at page 15, line 27 through page 16, line 5. In particular, the preferred, more preferred, and most preferred SEQ ID NO:3 variants (at least about 80%, at least about 90%, and at least about 95% amino acid sequence identity to SEQ ID NO:3) are described, for example, at page 18, lines 1-4. In particular, the preferred, more preferred, and most preferred SEQ ID NO:4 variants (at least about 80%, at least about 90%, and at least about 95% polynucleotide sequence identity to SEQ ID NO:4) are described, for example, at page 18, lines 11-21. The Specifications states that PAWES-2 can be "obtained from **any species**, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether **natural**, synthetic, semi-synthetic, or recombinant." (e.g., at page 6, lines 20-22; emphasis added). Incyte clones in which the nucleic acids encoding the human PAWES-2 were first identified and libraries from which those clones were isolated are described, for example, at page 17, lines 10-15 of the Specification. Chemical and structural features of PAWES-2 are described, for example, on page 17, lines 16-24. Given SEQ ID NO:3, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:3 at least 90% identical to SEQ ID NO:3. Given SEQ ID NO:4, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:4 at least 90% identical to SEQ ID NO:4. The Specification describes (e.g., page 11, lines 5-21 and page 45, lines 2-19) how to use BLAST and other methods to determine whether a given sequence falls within the "at least 90% identical" scope. Immunogenic fragments are described in the Specification, e.g, at page 9, lines 3-6.

There simply is no requirement that the claims recite particular variant and fragment polypeptide or polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants and fragments are defined in terms of SEQ ID NO:3 ("An isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of. . . b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, and c) an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five

amino acid residues in length." The polynucleotide variants and fragments are defined in terms of SEQ ID NO:4 ("An isolated polynucleotide selected from the group consisting of . . . b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4;" "An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 12.")

Because the recited polypeptide variants and fragments are defined in terms of SEQ ID NO:3, and the recited polynucleotide variants and fragments are defined in terms of SEQ ID NO:3 and SEQ ID NO:4, the precise chemical structure of every polypeptide variant and fragment and every polynucleotide variant and fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention. Appellants further submit that given the polypeptide sequence of SEQ ID NO:3 and the polynucleotide sequence of SEQ ID NO:4, it would be redundant to list specific fragments. The structures of SEQ ID NO:3 and SEQ ID NO:4 provide the blueprint for all fragments thereof. Listing all possible fragments of SEQ ID NO:3 and SEQ ID NO:4 is, thus, a superfluous exercise which would needlessly clutter the Specification. Examples of SEQ ID NO:3 and SEQ ID NO:4 fragments are given on page 17, lines 24-26. Accordingly, the Specification provides an adequate written description of the recited polypeptide and polynucleotide sequences.

I. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional

characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claims 3 and 12 recites chemical structure to

define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
>
> a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3,
>
> b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, and
>
> c) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length.
>
> 12. An isolated polynucleotide selected from the group consisting of:
>
> a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,
>
> b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,
>
> c) a polynucleotide having a sequence completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a), and
>
> d) a polynucleotide having a sequence completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3 and SEQ ID NO:4. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. Moreover, such functional recitations as are included add to the structural characterization of the recited polynucleotides and polypeptides. The polynucleotides and polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

II. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." (Office Action mailed December 31, 2002, page 18.) Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Reference No. 28, previously also cited in the Response filed March 31, 2003). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to PAWES-2 proteins related to the amino acid sequence of SEQ ID NO:3. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as PAWES-2 proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:3. The "variant language" of the present claims recites, for example, polypeptides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:3" (note that SEQ ID NO:3 has 332 amino acid residues). This variation is far less than that of all potential PAWES-2 proteins related to SEQ ID NO:3, i.e., those PAWES-2 proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:3.

In any case, "function" is irrelevant to the use of the recited polypeptide variants and polynucleotide variants, e.g., in toxicology testing (see for example, Specification, page 37, line 25 through page 41, line 27 and page 42, line 28 through page 43, line 16).

III. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of April 29, 1998. Much has happened in the development of recombinant DNA technology in the 18 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:3 and SEQ ID NO:4, and the additional extensive detail provided by the subject application, the present inventors were in possession of the recited polynucleotides and polypeptides at the time of filing of this application.

IV. The Office Action mailed December 31, 2002 states that "[a]bsent evidence to the contrary, the sequence elected for examination is deemed to be an incomplete cDNA. Because the cDNA that corresponds to the SEQ ID NO mentioned in the claim is not full-length, a sequence prepared from undefined parts of a cDNA clone will not comprise the entire coding region of any particular gene, nor is it clear the partial sequence is even in frame to encode a polypeptide" (Office Action mailed December 31, 2002, page 16).

SEQ ID NO:4, however, encompasses a complete coding region of a gene, and this coding region encodes a polypeptide of SEQ ID NO:3. It is axiomatic that a polynucleotide of SEQ ID NO:4 encodes a polypeptide of SEQ ID NO:3. One of ordinary skill in the art would be able to routinely determine the extent of the coding region of SEQ ID NO:4 by looking for start codons and stop codons sharing the same reading frame in the polynucleotide. Translation of the limited number of possible coding regions of SEQ ID NO:4 would reveal which one corresponds

to the polypeptide sequence disclosed in SEQ ID NO:3. All of these determinations are routine in the art, and do not require undue experimentation. Thus, Appellants had full possession of not only SEQ ID NO:4 and SEQ ID NO:3 at the time of filing, but also the coding region of SEQ ID NO:4 which encodes SEQ ID NO:3. It is well known to one of ordinary skill in the art that the coding region of a gene can be used to produce the encoded polypeptide, whether or not the 5' and 3' regulatory regions and untranslated regions are present. For example, the coding sequence of SEQ ID NO:4 could be cloned into an expression vector and the coding sequence expressed in an appropriate host organism. For example, the specification discloses that "[f]or expression of PAWES in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element." (e.g., at page 52, lines 14-18).

The Office Action mailed December 31, 2002 also alleges that Appellants did not possess the claimed invention because polynucleotides comprising SEQ ID NO:4 include "full length" genes which are not adequately disclosed in the specification. That is, the Office Action mailed December 31, 2002 asserts that the 5' and 3' regulatory regions and untranslated regions of the gene must be described to fulfill the written description requirements. Such a position is improper.

Appellants respectfully point out that these "full length" genes are not explicitly recited in the claims. Only the specific polynucleotides recited in the claims are at issue, and these polynucleotides are adequately described in the specification. Although the phrase "comprising" "does not exclude additional, unrecited elements or method steps" (M.P.E.P. § 2111.03), the use of this phrase does not result in the inclusion of any arbitrary element in the scope of the claim if such elements are not specifically recited. In this case, the claimed polynucleotides **do not** explicitly include the 5' and 3' regulatory regions and untranslated regions of the gene, and Appellants **are not** explicitly claiming the "full length" gene (although Appellants are hereby **not** expressly disclaiming the "full length" gene, or any polynucleotide including the 5' or 3' regulatory regions or untranslated regions of the gene). There is simply no requirement for the specification to include a detailed description of elements which are not explicitly recited by the

claims.

In the Final Office Action on page 28, the Examiner states that the "rejection is not drawn to SEQ ID NO:4, but rather to the claimed variants which, as broadly written, read on genomic DNA for the reasons of record" and that "[s]ince the claims are open and read on genomic DNA, inclusion of genomic elements in determining the scope of the claims is proper."

Appellants respectfully submit that the instant claims do not encompass genomic polynucleotide sequences. They disclose purified polynucleotide sequences that directly encode the recited polypeptides, without requiring excision of any intronic sequence. The claimed polynucleotides encompass sequences that directly encode (codon by codon) the recited polypeptides. Any other reading of the claim is strained, at best. This does not mean that 5' or 3' polypeptide extensions are not literally encompassed, but rather that no sequences containing intervening intronic sequences of any significance are encompassed.

Furthermore, the claims which recite the mathematical method of defining (and thus evaluating) encompassed naturally occurring variants do not read on genomic sequence including introns.

The rejected claims do not recite the words "genomic DNA" in describing the claimed polynucleotide sequences. Independent Claim 3 is directed to "*[a]n isolated polynucleotide* encoding a polypeptide selected from the group consisting of: a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, and c) an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length." Independent claim 12 is directed to "[*a]n isolated polynucleotide* An isolated polynucleotide selected from the group consisting of: a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4, b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4, c) a polynucleotide having a sequence completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a), and d)

a polynucleotide having a sequence completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b)."

The plain meaning of the words in Claims 3 and 12, particularly as taken in view of the state of the art (including literally thousands of other gene patents issued by the USPTO that use essentially identical language to the instant Claims 3 and 12), and the disclosure in the specification make it clear that the claimed sequences do not encompass genomic DNA.

The Examiner (and the courts) are directed by *Genentech Inc v. The Wellcome Foundation Ltd.*, 31 USPQ2d 1161(Fed. Cir. 1994) to construe claims in such a way as to preserve validity, particularly when there is only one reasonable way of construing the claims asserted by Appellants during prosecution. As the Federal Circuit said:

> An appropriate method for resolving the issue [the proper scope of the phrase "human tissue plasminogen activator" appearing in the claims] is to avoid those definitions upon which the PTO could not reasonably have relied when it issued the patent. That is an appropriate method to follow because it avoids the possibility of an applicant obtaining in court a scope of protection which encompasses subject matter that, through the conscious efforts of the applicant, the PTO did not examine. An applicant should not be able deliberately to narrow the scope of examination to avoid during prosecution scrutiny by the PTO of subject matter with the objective of more quickly obtaining a patent (or avoiding the risk of an estoppel), and then obtain in court, either literally or under the doctrine of equivalents, a scope of protection which encompasses that subject matter. See *North American Vaccine Inc.*, 7 F.3d at 1577, 28 USPQ2d at 1337. [footnote omitted]

Appellants expressly assert that the Examiner's concern that the scope of Appellants' claims might be extended, by torturous claim construction, to include genomic sequences not supported in the specification is therefore misplaced, as Appellants have clearly not only disclaimed it by the plain meaning of the claims, but also expressly herein. No court or member of the public could reasonably read them so broadly.

V. The Examiner alleges that "it is not true that one could find in nature any and all possible changes within a given gene, and the specification has described not a single naturally occurring variant of SEQ ID NO:4. . . not a single sequence disclosed that is obtained from another biological species." (Final Office Action, page 30.) Appellants are not claiming "any and all possible changes within a given gene." Appellants claim polynucleotides comprising a naturally

occurring polynucleotide sequence at least 90% identical to SEQ ID NO:4 and polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:3.

VI. The Examiner questions the truth of Appellants' statement on page 42 of the Response filed March 31, 2003 that "one of ordinary skill in the art would recognized [*sic*: recognize] naturally-occurring variants of SEQ ID NO:3 having 90% sequence identity to SEQ ID NO:3." (Final Office Action, page 30.) The Examiner alleges that "[o]ne could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO:3, but that same person, handed a protein in a test tube, would have no way of determining whether that protein were 'naturally occurring.' The same applies to the nucleic acid of SEQ ID NO:4." (Final Office Action, page 30.)

Appellants note that sequence information is not provided in a vacuum. Identification of the source of the sequence will typically allow one to determine if it is naturally-occurring. Also, attempted deceit to hide the source will not preclude infringement.

VII. The Examiner attempts to distinguish the *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) cases from the instant case as "the claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions" and that "[i]n this case, Applicants claims require no such conserved function. (Final Office Action, page 31.) In *Fiers*, the Examiner contends, "the person of ordinary skill in the art would immediately recognize that any and all species within the metes and bounds of 'A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide,' would encode proteins with *greater* than the 90% identity claimed by Applicants; the person of ordinary skill in the art would not expect to find that great an amount of variation within a single species, while still meeting the functional limitation of being a human fibroblast interferon-beta polypeptide." (Final Office Action, page 31, emphasis in original.) Appellants note first that the Examiner has provided only personal opinion to support this argument, without either evidence or sound scientific reasoning. Second, in the instant case the claimed species are

described by not only their comprising "naturally-occurring" sequences but also by their percentage sequence identity with either SEQ ID NO:3 or SEQ ID NO:4. A structure is provided in the instant case by the recitation of a particular nucleotide or amino acid sequence, while it was not in the *Fiers* and *Lilly* claims.

VIII. The Examiner contends that "[w]hile 90% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function." (Final Office Action, page 33.) The Examiner further alleged that "[t]here is no description about the function of the gene nor the protein encoded thereby, such as would allow one of skill to predict what portions of the disclosed sequence would be expected to be conserved." (Final Office Action, page 29.) As the claimed variants are not described by their having the same "function" as SEQ ID NO:3 or SEQ ID NO:4, the Examiner's arguments are not relevant to the written description issue.

Nevertheless, Appellants note that it is well known in the art that sequence similarity is predictive of similarity in functional activity. Furthermore, Hegyi and Gerstein (H. Hegyi and M. Gerstein, "Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins," Genome Research (2001) 11: 1632-1640; Reference No. 29) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3." (Hegyi and Gerstein, page 1635.) Hegyi and Gerstein also concluded that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "[t]he probability that the functions are the same in this case was 91%." (Hegyi and Gerstein, page 1636.) Hegyi and Gerstein (page 1632) further note that

> Wilson et al. (2000) compared a large number of protein domains to one another in a pair-wise fashion with respect to similarities in sequence, structure, and function. Using a hybrid functional classification scheme merging the ENZYME and FlyBase systems (Gelbart et al. 1997; Bairoch 2000), they found that precise function is not conserved below 30–40% identity, although the broad functional class is usually preserved for sequence identities as low as 20–25%, given that the sequences have the same fold. Their survey also reinforced the previously established general exponential relationship between structural and sequence similarity (Chothia and Lesk 1986).

The polypeptides encoded by the claimed polynucleotides share more than 90% sequence identity with the SEQ ID NO:3 polypeptide, well above the thresholds described in the Hegyi and Gerstein article cited above. Therefore, there is a reasonable probability that the SEQ ID NO:3 polypeptide variants would have the same function as the SEQ ID NO:3 polypeptide.

IX. Summary

The Final Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Final Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3 or SEQ ID NO:4. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides and polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Final Office Action.

Issue Seven: Novelty Rejection of Claims 3, 6, 7, and 9

The Examiner rejected Claims 3, 6, 7, and 9, alleging that the claimed polynucleotides encoding immunogenic fragments of SEQ ID NO:3 wherein said fragment is at least five amino acid residues in length, were anticipated by U.S. Patent 5,683,998. The Examiner stated that "review of the sequence comparison, us-09-848-852-3.rni result 2, of record, clearly shows that the reference teaches a polynucleotide that encodes five amino acids of SEQ ID NO:3." (Final Office Action, page 34.)

Appellants appeal this rejection, as the Examiner appears to be misinterpreting the "sequence comparison, us-09-848-852-3.rni result 2, of record." This sequence comparison shows the results of an analysis which compared the SEQ ID NO:3 polypeptide sequence with the translation of the U.S. Patent 5,683,998 polynucleotide sequence. When a translated codon

of the U.S. Patent 5,683,998 polynucleotide sequence encodes an amino acid residue **identical** with a residue in the SEQ ID NO:3 polypeptide sequence, **three solid lines** connect the amino acid residue of the SEQ ID NO:3 polypeptide with the U.S. Patent 5,683,998 polynucleotide sequence: e.g., residue 9 of SEQ ID NO:3 (Gly) aligned with the amino acid encoded by bases 537-539 (GGA) of the U.S. Patent 5,683,998 polynucleotide sequence. The codon "GGA" encodes the amino acid residue "Gly", thus three solid lines connect Gly9 in SEQ ID NO:3 with GGA (537-539) in the U.S. Patent 5,683,998 polynucleotide sequence. See Diagram A below and the marked up copy (Reference No. 30) of the "sequence comparison, us-09-848-852-3.rni result 2, of record."

However, when the translated codon of the U.S. Patent 5,683,998 polynucleotide sequence encodes an amino acid residue that is a **conservative substitution (i.e., non-identical)** with a residue in the SEQ ID NO:3 polypeptide sequence, **three dotted lines** connect the amino acid residue of the SEQ ID NO:3 polypeptide with the U.S. Patent 5,683,998 polynucleotide sequence: e.g., residue 11 of SEQ ID NO:3 (Ile) aligned with the amino acid encoded by bases 543-545 (CTT) of the U.S. Patent 5,683,998 polynucleotide sequence. The codon "CTT" encodes the amino acid residue "Leu." The sequence analysis program considers Leu to be a conservative substitution with respect to the Ile in the SEQ ID NO:3 polypeptide sequence. Therefore, three dotted lines connect Ile11 in SEQ ID NO:3 with CTT (543-545) in the U.S. Patent 5,683,998 polynucleotide sequence. See Diagram A below and the "sequence comparison, us-09-848-852-3.rni result 2, of record."

```
Qy    9     GlyThrIleTrp. . .
            |||   :::|||
Db    537   GGACCACTTTGG. . .
```

DIAGRAM A

The regions of the "sequence comparison, us-09-848-852-3.rni result 2, of record" that the Examiner appears to be misinterpreting are the five residue regions from Asp174-Glu178 and from Ala254-Gln258, as shown in Diagram B below and in the attached marked up copy of the

"sequence comparison, us-09-848-852-3.rni result 2, of record."

```
Qy    174  AspThrValProGlu
           ||||||:::||||||
Db    1186 GACACGATTCCAGAG

Qy    254  AlaLysTyrLeuGln
           ||||||:::::::::
Db    1339 GCCAAGTTTGTCGAA
```

DIAGRAM B

The region from Asp174-Glu178 of SEQ ID NO:3 contains (a) two consecutive amino acid residues, Asp174 and Thr175, which are identical to the amino acid residues encoded by bases 1186-1188 (GAC encoding Asp) and 1189-1191 (ACG encoding Thr) of the U.S. Patent 5,683,998 polynucleotide sequence; (b) one amino acid residue, Val176, is a **conservative (non-identical)** amino acid substitution with respect to the amino acid residue encoded by bases 1192-1194 (ATT encoding Ile) of the U.S. Patent 5,683,998 polynucleotide sequence; and (c) two consecutive amino acid residues, Pro177 and Glu178, which are identical to the amino acid residues encoded by bases 1195-1197 (CCA encoding Pro) and 1198-1200 (GAG encoding Glu) of the U.S. Patent 5,683,998 polynucleotide sequence. Therefore, the U.S. Patent 5,683,998 polynucleotide sequence from bases 1186-1201 does not anticipate a polynucleotide encoding an immunogenic fragment of a polypeptide consisting of an amino acid sequence of SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length.

The region from Ala254-Gln258 of SEQ ID NO:3 contains (a) two consecutive amino acid residues, Ala254 and Lys255, which are identical to the amino acid residues encoded by bases 1339-1341 (GCC encoding Ala) and 1342-1344 (AAG encoding Lys) of the U.S. Patent 5,683,998 polynucleotide sequence; and (b) three consecutive amino acid residues Tyr256, Leu257, and Gln258 which are **conservative (non-identical)** amino acid substitutions with respect to the amino acid residues encoded by bases 1345-1347 (TTT encoding Phe), 1348-1350 (GTC encoding Val), and 1351-1353 (GAA encoding Glu) of the U.S. Patent 5,683,998

polynucleotide sequence. Therefore, the U.S. Patent 5,683,998 polynucleotide sequence from bases 1339-1353 does not anticipate a polynucleotide encoding an immunogenic fragment of a polypeptide consisting of an amino acid sequence of SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length.

Therefore, the U.S. Patent 5,683,998 polynucleotide sequence does not encode an immunogenic fragment of SEQ ID NO:3 wherein said fragment is at least five amino acid residues in length. Therefore, U.S. Patent 5,683,998 does not anticipate Claims 3, 6, 7, and 9. Appellants respectfully request that the novelty rejection of Claims 3, 6, 7, and 9 be overturned.

(9) CONCLUSION

Appellants request that the rejections of the claims on appeal be reversed for at least the above reasons.

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Final Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[6] to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specification as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

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[6] "The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

This brief is enclosed in triplicate.

Respectfully submitted,

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Enclosures:
Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q

Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132

Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E

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APPENDIX - CLAIMS ON APPEAL

3. (As Once Amended) An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3,

b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, and

c) an immunogenic fragment of a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3, wherein said fragment is at least five amino acid residues in length.

4. (As Once Amended) An isolated polynucleotide of claim 3 encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3.

5. (As Once Amended) An isolated polynucleotide of claim 4, comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

9. (As Once Amended) A method for producing a polypeptide, the method comprising:

a) culturing the cell of claim 7 under conditions suitable for expression of the polypeptide, and

b) recovering the polypeptide so expressed.

10. A method of claim 9, wherein the polypeptide has a sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3.

12. (As Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,

b) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4,

c) a polynucleotide having a sequence completely complementary to a polynucleotide of a) over the entire length of the polynucleotide of a), and

d) a polynucleotide having a sequence completely complementary to a polynucleotide of b) over the entire length of the polynucleotide of b).

13. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 12.

49. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:4.